UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,680	01/25/2002	Teddy Kosoglou	CV01492K	9993

24265 7590 02/25/2008

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

EXAMINER	
HUI SAN MING R	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
02/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,680	KOSOGLOU ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,12-17,21-42,45,47 and 48* is/are pending in the application.

4a) Of the above claim(s) *4-10,12-17,21-34,38-41 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,35-37,42-45 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-4-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed December 4, 2007 has been entered.

Claims 1, 3-10, 12-17, 21-42, 45, 47-48 are pending. Claims 4-10, 12-17, 21-34, 38-41, and 48 have been withdrawn from consideration.

Claims 1, 3, 35-37, 42, 45, and 47 have been examined herein to the extent they read on the elected invention and species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 35-37, 42-45, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenblum et al. (EP 0720 599, reference CA from IDS received January 21, 2003), and Ullah (WO 99/47123 from IDS received January 21, 2003) in view of Frei (Proc Soc Exp Biol Med. 1999 Dec; 222(3): 196-204).

Rosenblum et al. teaches a composition comprising the compound of Formula (II), lactose, and magnesium stearate (See particularly claims 8, and 9, page 24, example 6, page 29, Examples A and B). Rosenblum et al. also teaches the active compounds therein, including the racemic mixture of compound of Formula (II), can be formulated into a tablet (See Example A and B in page 29). Rosenblum et al. also teaches the effective dosage of compound of Formula (II) as 5 to 1000mg per day (See page 17, paragraph 0065). Rosenblum et al. also teaches the active compounds therein can be combined with HMG-CoA reductase inhibitors, preferably simvastatin, for reducing cholesterol and the risk of artherosclerosis (See 5, paragraph 0028, also claims 16 and 17).

Ullah teaches a composition comprising statins, such as simvastatin, in combination with aspirin, for cholesterol lowering and treating or reducing the risk of developing atherosclerosis (See the abstract, also page 1, lines 14-18). Ullah teaches the dosage for aspirin as 50-650mg (See page 5, lines 34-37).

The primary references do not expressly teach the composition comprising the compound of formula (II) herein, aspirin, and simvastatin together. The primary references do not expressly teach antioxidants be incorporated into the composition containing compound of formula (II) herein, aspirin, and simvastatin.

Frei teaches antioxidants, such as vitamin C and vitamin E, as useful in inhibit the atherogensis and normalize the vascular functions (See the abstract, page 198, col. 2, second paragraph, also page 199, col. 1, second paragraph, page 201, col. 2, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the compound of Rosenblum into the composition of Ullah. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate antioxidant into the composition containing compound of formula (II) herein, aspirin, and simvastatin.

One of ordinary skill in the art would have been motivated to combine the compound of Rosenblum into the composition of Ullah. Combining composition of Rosenblum and that of Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

One of ordinary skill in the art would have been motivated to incorporate antioxidant into the composition containing compound of formula (II) herein, aspirin, and simvastatin. Vitamin C, an antioxidant, is known as useful to inhibit the development of atherosclerosis. Combining vitamin C with composition containing compounds of Rosenblum and/or Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

Response to Arguments

Applicant's arguments averring the unexpected results, along with the declaration by Dr. Chintala, filed December 4, 2007 have been considered, but are not found persuasive. Examiner notes that it is applicant's burden to demonstrate unexpected

results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, the dosage claimed is not commensurate with the dosage used in the experiment. There is only one single dosage used for aspirin and one dosage for ezetimibe and yet the claims recite a very large range of both agents. It is not clear how one single dosage can extrapolate to a vast range of active. There is no rationale as to how the dosage of ezetimibe be expanded to a broad range as claimed. The rationale for expanding the dosage of aspirin is not convincing. For example, various references were cited in attempt to provide reasoning for the range of dosage recited in the claims; however, the herein claimed dosage range is not the normal dosage range for antiplatelet activity. Moreover, it is clear that different patient populations would need different dosages of aspirin. It is also true for different rat models. Killackey et al. reported that 200mg/kg of aspirin would be required to prevent carotid artery thrombosis and that 100mg/kg is insufficient. Therefore, one of ordinary skill in the art would see that the dosages of aspirin would be depending on what patient populations are being treated. In the instant case, only one rat model, one dosage of aspirin, and one dosage of ezetimibe were used. One cannot just simply extrapolate the dosage from one

dosage point to a wide range based on what is generally known because it should be an unexpected result. The dosage recited in the claims should be corresponding to the unexpected benefit of antiplatelet activities used demonstrated in Dr. Davis' declaration filed November 5, 2005. Accordingly, the claims are still considered properly rejected under 35 USC 103(a).

Applicant's arguments filed December 4, 2007 averring the lack of motivation provided by the cited prior art to combine the herein claimed agents (whether it is ezetimibe and aspirin with the statins or ezetimibe and aspirin with vitamin or antioxidants [without the statins]) have been considered, but are not found persuasive. Firstly, the examiner appreciates the applicant pointing out that some of the claims recite a composition comprises ezetimibe and aspirin with the statins and claim 42 recites a composition comprises ezetimibe and aspirin with vitamins or antioxidants. However, the examiner respectfully notes that although some claims do not recite the incorporation of statins or vitamins or antioxidants, they are not excluding any components because the claims are opening-ended claims which recite the transitional phrase "comprising". The claims clearly permit any additional components to be added to the herein claimed composition. Secondly, regardless of statins or vitamin being incorporated into the herein claimed ezetimibe-aspirin composition, the basis of the rejection under 35 USC 103(a) is the same: the herein claimed agents are known to be useful in reducing the risk of cardiovascular diseases such as atherosclerosis. Therefore, combining these agents into a single composition useful for the very same purpose would be considered obvious, absent evidence to the contrary (See *In re*

Kerkhoven 205 USPQ 1069 (CCPA 1980)). Examiner notes that the basis to combine is not based on the agents having same mechanism of action. The basis is rather they are known to have the same therapeutical use in the art. Therefore, possessing the teachings of the cited prior arts, one of ordinary skill in the art would have been motivated to combine the herein claimed actives into a single composition useful for the very same purpose (See *Kerkhoven* supra).

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/San-ming Hui/
Primary Examiner, Art Unit 1617